Incorporating information from adults into pediatric trial design:
A Case Study of Guillan-Barré Syndrome

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The Question

- Is intravenous immune globulin (IVIg) of equal or superior efficacy to plasma exchange in treatment of pediatric Guillan-Barré syndrome (GBS)?

Background: Pediatric GBS

- An acute polyneuropathy of uncertain etiology, likely due to molecular mimicry, characterized by weakness, sensory loss, and areflexia.
- Validated Grading Scale:
  - Grade 0: Normal
  - Grade 1: Minor signs or symptoms
  - Grade 2: Able to walk 5 meters w/o support
  - Grade 3: Walk 5 meters with support
  - Grade 4: Chairbound
  - Grade 5: On ventilator for all or part of day
  - Grade 6: Dead

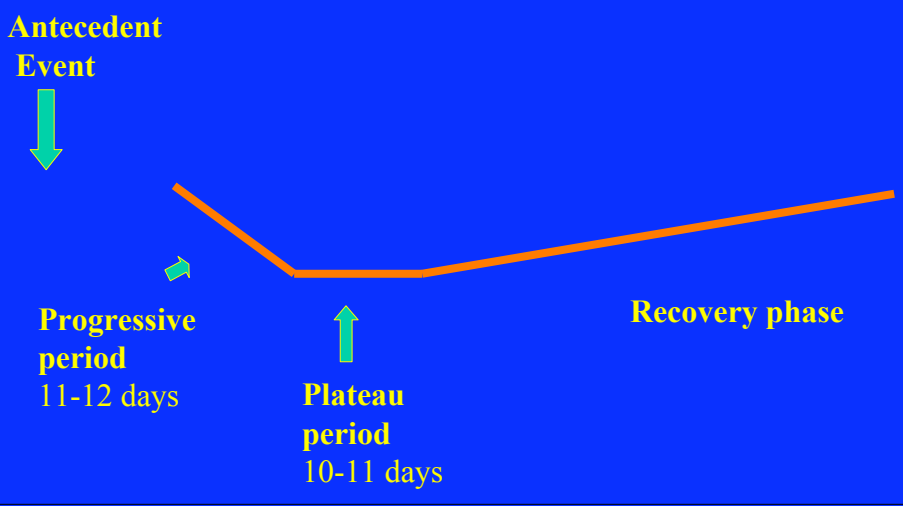
Background: Pediatric GBS

- Rare: 3-10/Million annually
- 200-600 cases/year in US <17 yrs., Stage 3/4 about 50% of total.
- Almost all children recover with minimal sequelae.
- Children in Grades 1-2 are typically not hospitalized. Grades 3-5 all are hospitalized.

Adult vs. Pediatric GBS

- No known difference in pathophysiology or clinical course, except that children recover more quickly, almost never die, and have fewer serious sequelae.

Natural History of Pediatric GBS



Plasma Exchange (PE)

- Involves removing blood from body, removing plasma component and returning it, reconstituted with saline and/or albumin.
- Requires a central catheter and usually inpatient care.
- Costs ca $10K per full course of treatment.
- Mechanism of action is unclear; assumed to be removal of antibodies and cytokines.
- Most serious side effects are bleeding, infection, pneumothorax, and cardiovascular instability.

IV Immune Globulin (IVIg)

- Involves IV infusions once daily for 5 days.
- Cost is similar to plasmapheresis.
- Mechanism of action is unclear.
- Main side effects are flu-like symptoms or allergy, reduced by pretreatment or slowing infusion.
- Therapeutic equivalence of different formulations likely but not certain.

Goal of Treatment

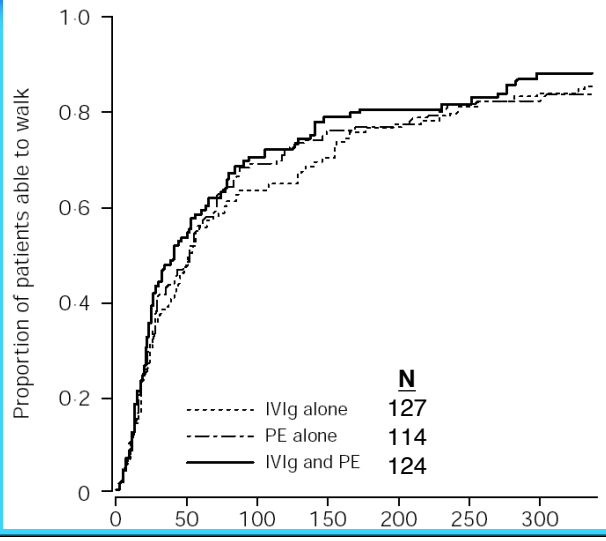
- Accelerate recovery to reduce time in hospital, on a ventilator and unable to walk. In adults, treatment reduces hospital costs.

What do we know in adults?: PE vs. Placebo

- Two RCTs of plasma exchange versus placebo showed identical effects on median time to unaided walking (Time to grade 2):

Study	N (age)	Placebo	PE	HR	P-value
French GBS Study (1985)	245 (>16)	111 d	70 d	0.63	<0.001
GBS Study Group (1985)	220 (>12)	85 d	53 d	0.62	<0.001

What do we know in Adults? : PE vs. IVIg



PSGBS Study Group, Lancet 1997; **349**: 225-230

Median time to walking:
IVIg: 51 d
PE: 49 d
IVIg+PE: 45 d

HR IVIG vs PE:
1.04, CI 0.8 to 1.4

What do we know in Adults? : PE vs. IVIg

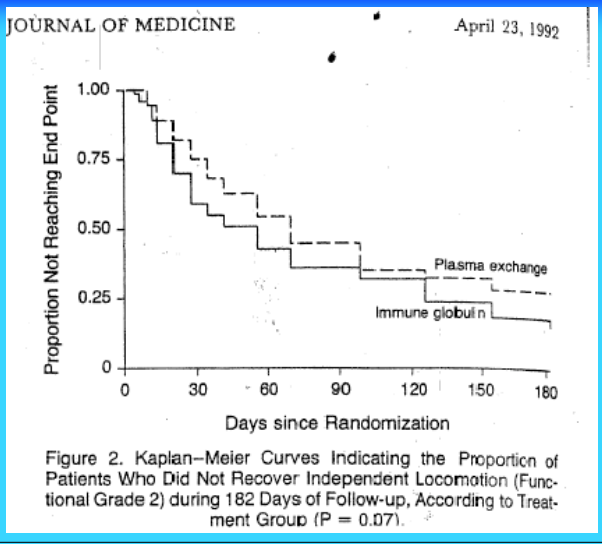


Figure 2. Kaplan–Meier Curves Indicating the Proportion of Patients Who Did Not Recover Independent Locomotion (Functional Grade 2) during 182 Days of Follow-up, According to Treatment Group (P = 0.07).

Van der Meché, NEJM 1992

Median time to walking:
IVIg: 55 d (N=74)
PE: 69 d (N=73)

HR:
0.80, CI 0.62 to 1.02, p=0.07

Meta-analytic average of two PE vs. IVIg studies:
HR = 0.91, CI 0.75 to 1.1

What do we know in children?

- Five case series/natural history studies of untreated pediatric GBS patients
- Four case series of children treated with PE compared to historical controls.

What do we know in children? : Natural history studies

Author	N	Median	Mean	S.D.
Korinthenberg 1996	56	40 days	45.4	24.7
Paradiso 1999	37		58.7	44.0
Epstein 1990	14		60.2	43.6
Lamont 1991	18	43 days		
Graf 1999	9		50.0	29.0

Weighted mean: 48 days, CI: 43 to 52

What do we know in children? : PE vs. Historical Control Studies

Author	Mean treated (N)	Mean untreated (N)	HR	S.D.
Epstein 1990	24 (9)	60 (14)	0.4	0.17-0.93
Lamont 1991	17 (6)	43 (18)	0.4	0.15 - 0.99
Jansen 1993	16 (8)	29 (11)	0.55	0.23 -1.37
Graf 1999	76 (6)	50 (9)	1.52	0.54 - 4.3
TOTAL		**RE model**	**0.58**	**0.32-1.0**

Parameters for planning pediatric study

- Non-inferiority study because:
  - Strong prior evidence that PE and IVIg are nearly equivalent.
  - Because IVIg therapy is less morbid, it would be preferred to PE with equal or slightly lower efficacy for QOL endpoint (i.e. time to walking).
- Estimate that median time to ambulation on PE is 24 days.

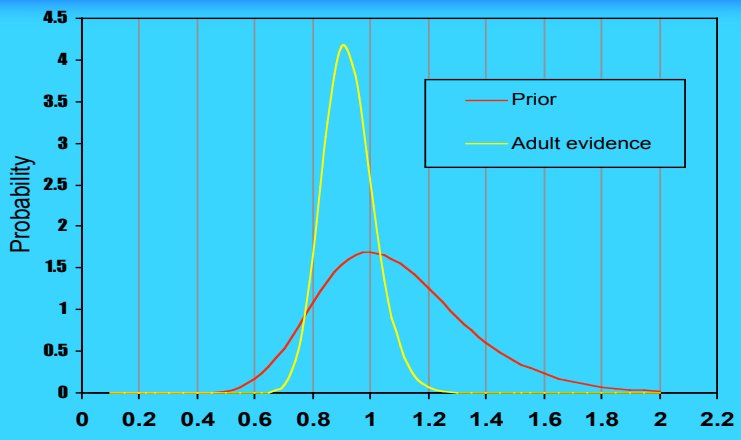
Parameters for planning pediatric study

- Chose non-inferiority margin of 7 days (i.e. median time 31 days on IVIg)
- Corresponds to HR=1.29 (=31/24)

Constructing prior for pediatric trials

- Since the meta-analytic HR for the adult trials is 0.91, CI 0.75 to 1.1, a pediatric trial would presumably not be needed if we thought the results in adults directly applied to kids.
- Downweight adult prior by a factor of about 2, and center at 1.0, to not introduce initial bias.
- Prior is HR=1.0, CI 0.6 to 1.67
- 2.5% prior probability that IVIg would extend time to walking by 2 weeks, 14% prior probability that it would be extended by 1 week over PE.
- Conversely, 14% prior that IVIg would *decrease* time to walking by 5.5 days, 2.5% on 9 day decrease.

Prior on IVIG vs PE Effect



Hazard ratio
(ratio of median recovery times)

Other prior facts

- Initial 86% probability that IVIg was not more than 7 days inferior.
- This prior is roughly equivalent to an RCT of 72 children showing IVIg-PE equivalence.
- The degree of evidence we will want is equivalence to a Bayes Factor of (95/5)÷(86/14) = 3

Design of trial with prior

- Stopping criteria: Stop when probability of non-inferiority exceeds 95%. Monitor after every 40 patients, max 160.

	True Median difference			
Sample size	**0**	**7 days**	**≤ 7 days, using prior**	**>7 days, using prior**
40	20%	4%	29%	2%
80	40%	8%	50%	3%
120	56%	10%	60%	4.7%
160	67%	12%	77%	5.2%

Other sample size approaches

- Sample size calculation for a superiority study with a MID of 1 week, 80% power, 2-sided alpha=5%, *N=450.*
- Sample size for a "non-inferiority study," 80% power, *N=750.*
- Sample size for superiority study with MID=14 days (i.e. HR = 38/24= 1.6) = *160.*

What have we gained?

- More certainty with fewer children based on a plausible, evidence-based prior.
- A way of making adult evidence count for kids, yet still require pediatric experimentation.
- A more “ethical” approach to testing in children.
- Allow flexibility in design, because all Bayesian designs can be adaptive, i.e. responsive to accumulating data.

What have we gained? (cont.)

- Way of formulating problem that encourages meaningful discussion among all stakeholders.
  - Degree of certainty needed after trial.
  - Degree of certainty before trial
    - ✓ quality, quantity, and relevance of adult data to children.
    - ✓ quality and quantity of children’s data.
  - Difference of interest. (Posterior probability curve can be used to calculate the probability of any difference.)
- Formality and explicitness about critical issues that persons using standard statistical approaches either hide, are unaware of, or deal with informally or in ad hoc ways.

Question

Can one apply a Bayesian approach where the a priori data comes from an adult patient population and the new data comes from a pediatric population?

Answer

- Yes, but only if the adult data is deemed relevant or informative.
- More empirical studies of this relevance need to be conducted, and ongoing.